Reduction of Logical Regulatory Networks by rewriting logical functions

Aurélien Naldi

2015/05/29

Outline

1. **Introduction**

2. **Model Reduction**
   - Dynamical Impact

3. **Selecting Reduced Components**

4. **Implementation and Applications**
   - GINsim: Definition and Analysis of Logical Models
   - CoLoMoTo: Improving Interoperability
   - Th differentiation

5. **Conclusion and Prospects**

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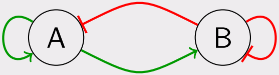
Logical Formalism

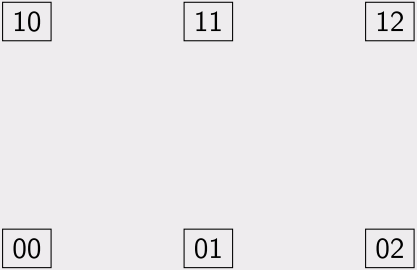
Regulatory Graph



- Components
- Interactions
- Logical functions

next(A): A & !B
next(B): A & !B:2

State Transition Graph



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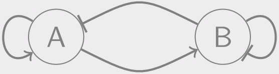

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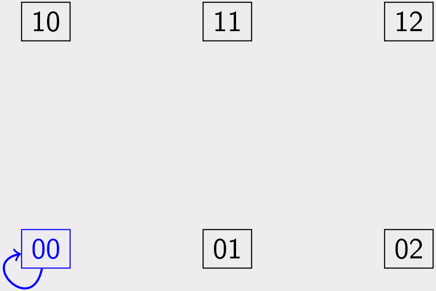

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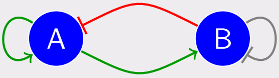

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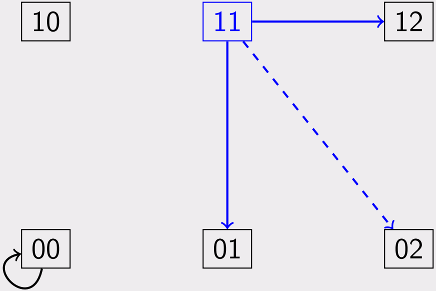
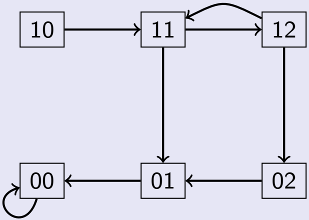
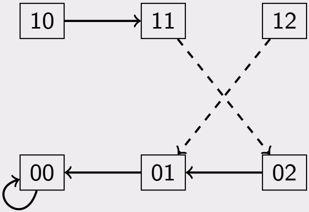


Dynamical Behaviour

Asynchronous



Synchronous



Other updatings

- Sequential
- Block-sequential
- Random walks

Properties

- Attractors
  stable states/oscillations
- Reachability

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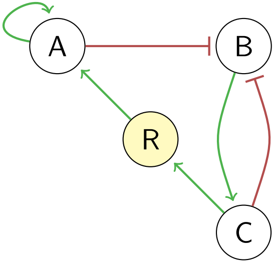
Model Reduction

Aim and properties

- Detailled reference model
- Multiple reductions
- Preserve feedback circuits
- Dynamical impact well understood

Removal of a Single Component

Definition of the reduced model:

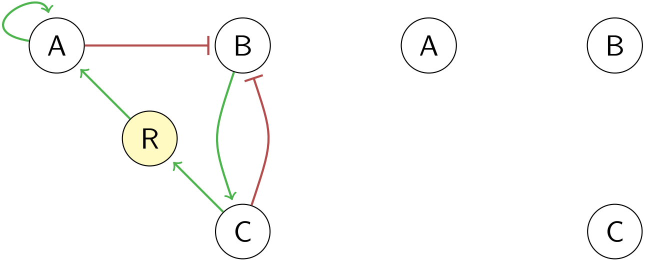


A Naldi et al. *Theor Comput Sci* (2011)

Removal of a Single Component

Definition of the reduced model:

- All components but *r*



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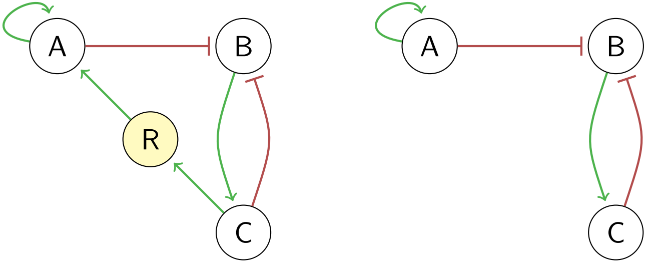

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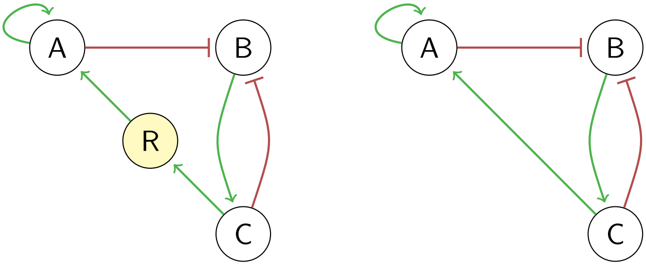

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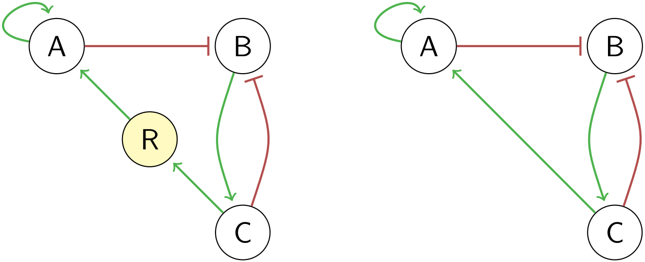


A Naldi et al. *Theor Comput Sci* (2011)

Removal of a Single Component

Definition of the reduced model:

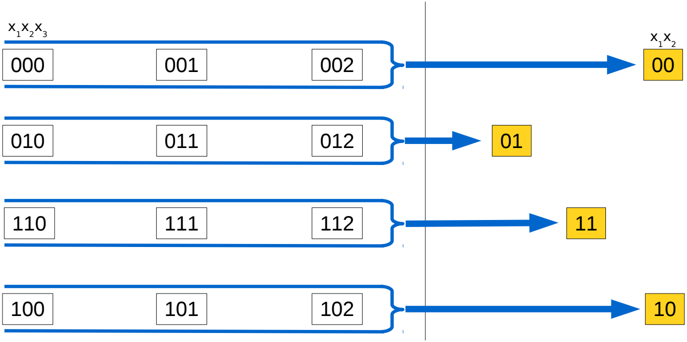
- All components but r
- Interactions between these components
- Regulators of r become regulators of its targets
- New logical functions for the targets of r

Replace constraints $r == v$ by parts of the function of r

All happens as if r reached its target value:
it can not be self-regulated

A Naldi et al. *Theor Comput Sci* (2011)

Dynamical Impact



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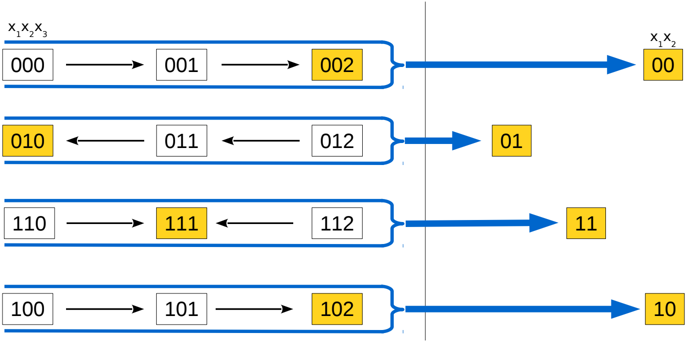

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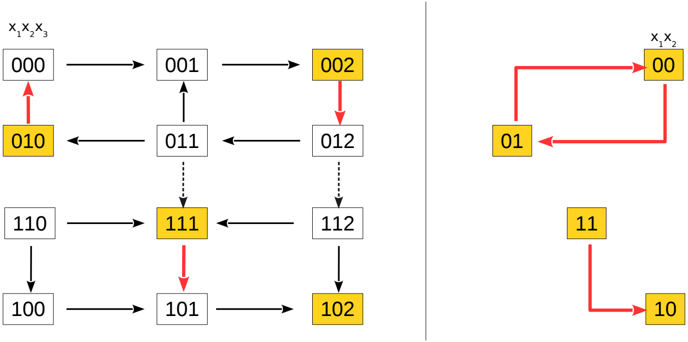

A Naldi et al. *Theor Comput Sci* (2011)

Order of multiple reductions

How to apply a series of reductions?

The order does not affect the result

"Representative states in Multiple directions" are unique

… but it may affect feasability

- A self-regulated state can not be reduced
- Reduction of his regulator may kill the loop
- finding a possible order is not trivial

Summary

Controlled dynamical impact

- Equivalence classes and representative states
- Preserve attractors
  - Same stable states
  - Stable oscillations in the same regions
  - May add new stable oscillations
- Reachability can be lost, not made up

Picking "good" reduced nodes is crucial

- "Fast" components
- Conservative reductions
  - no change in attractors
  - no change in reachability

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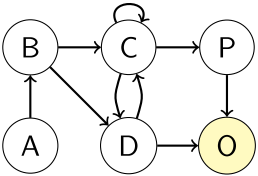
Reduction of output components

Output reduction

- No computation
- No impact
- Retrieve values



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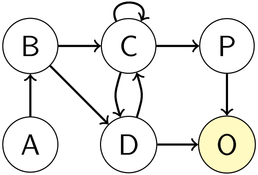
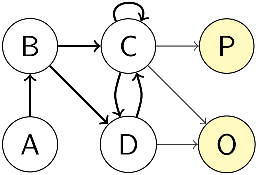


Extend to pseudo-outputs

- No impact
- Harder retrieval

⇒ Rewire the model: pseudo-outputs become outputs



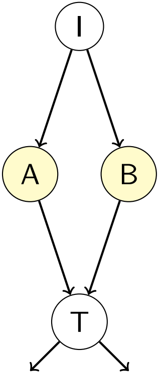
Rewiring: all functions only depend on core components

A Naldi, P Monteiro and C Chaouiya. *Computational Methods in Systems Biology*. 2012

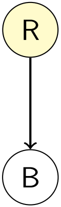
Reduction of pseudo-inputs

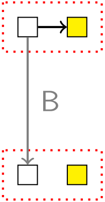
Propagation of pseudo-inputs

- Preserves attractors
- Reachability depends on initial condition



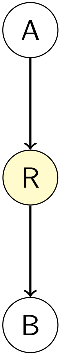
Looking for "safe" reductions

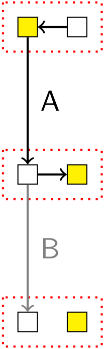




"Local" reachability loss related to targets of R: can't be avoided

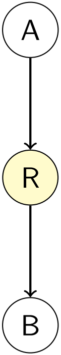
Looking for "safe" reductions

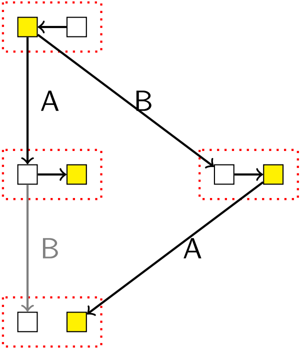




Better approach: look at longer paths with alternatives

Looking for "safe" reductions





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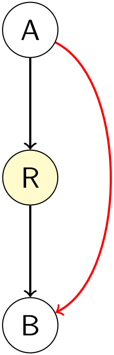
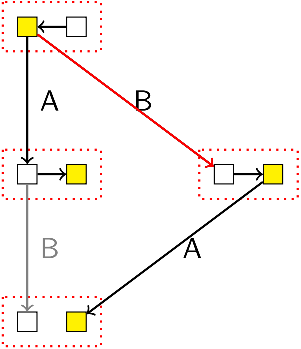
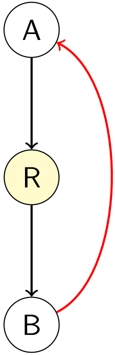
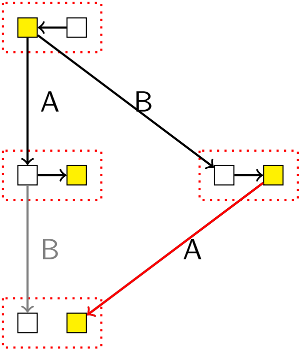




WIP: identification of motifs killing groups of alternative paths

Looking for "safe" reductions





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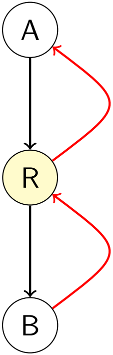

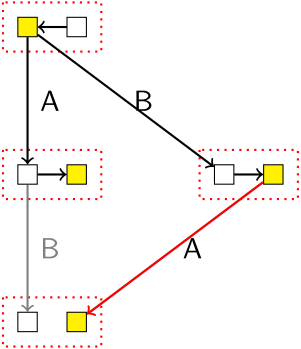

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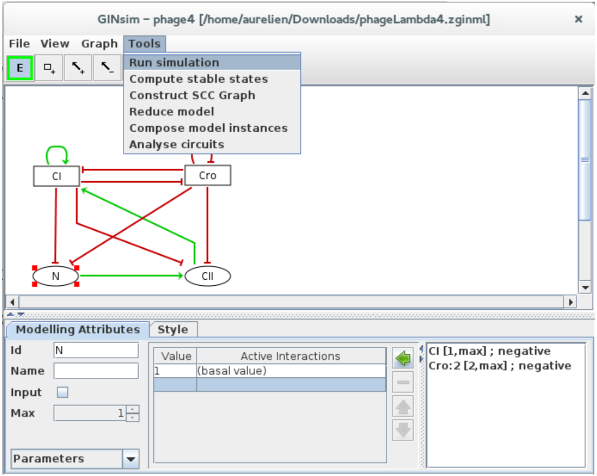
GINsim: Definition and Analysis of Logical Models



Id: N

Name:

Input: □

Max: 1

Value	Active Interactions
1	(basal value)

CI [1,max] ; negative
Cro:2 [2,max] ; negative

http://www.ginsim.org

A Naldi et al. *Bio Systems* (2009)

GINsim features

Model definition

- Interaction Graph & Logical functions
- Annotations
- Perturbations

Simulation

- Updating modes
- STG and HTG

Static Analysis

- Circuit Analysis
- Stable states

Import / Export

- Other modelling tools
- Documentation & Images

Miscellanous

- Scripting with Jython
- Open Source

A Naldi et al. *Bio Systems* (2009)

Using Multiple Tools for Logical Model Analysis

"Many" logical modelling tools available

Complete each other, but have no interoperability

Consortium for Logical Models Tools (CoLoMoTo)

- Exchanging models: SBML qual format
- Toolbox/converter: LogicalModel
- Take advantage of multiple tools

http://www.colomoto.org

https://github.com/colomoto

C Chaouiya et al. *BMC Syst Biol* (2013)

Related Tools

Formal: Attractor Identification

- Stable Motifs (J Zanudo & R Albert)
- Symbolic Steady States (H Klarner & H Siebert)

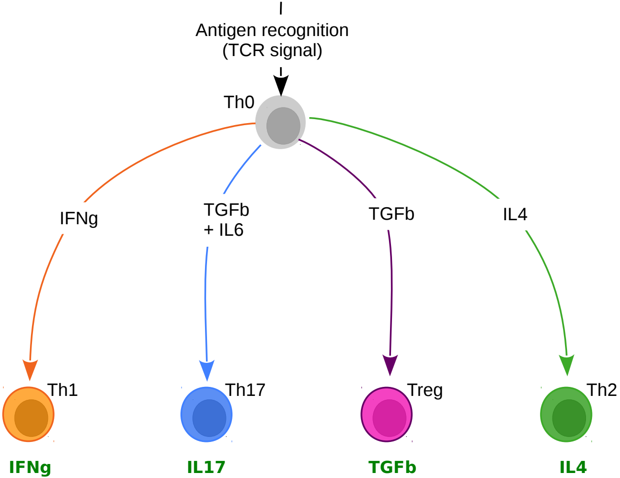
Simulation

- Model checking with NuSMV (P Monteiro)
- Reachability analysis with Pint (L Paulevé)
- Stochastic simulations with MaBoSS (G Stoll)
- Time delays with boolnet (C Müssel & H Kestler)
- Continuous simulations with SQUAD (L Mendoza & I Xenarios)

Model Optimization

- CellNopt (J Saez-Rodriguez)

Application: Th cell differentiation



A Naldi et al. *PLoS Comput Biol* (2010)

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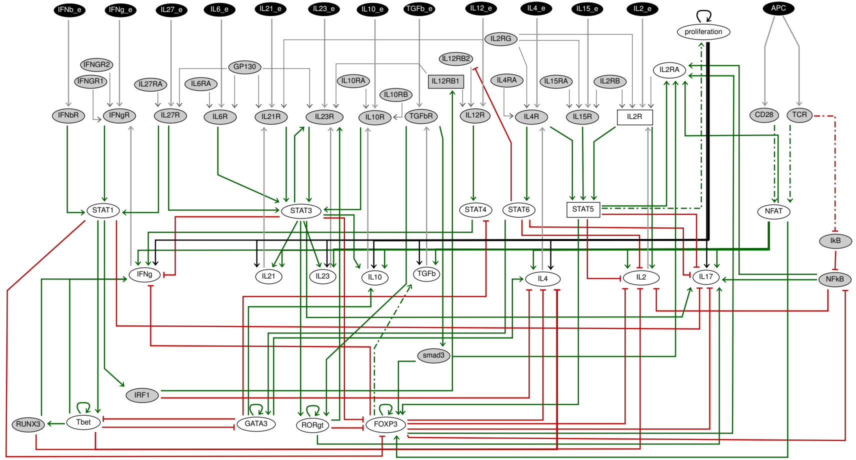

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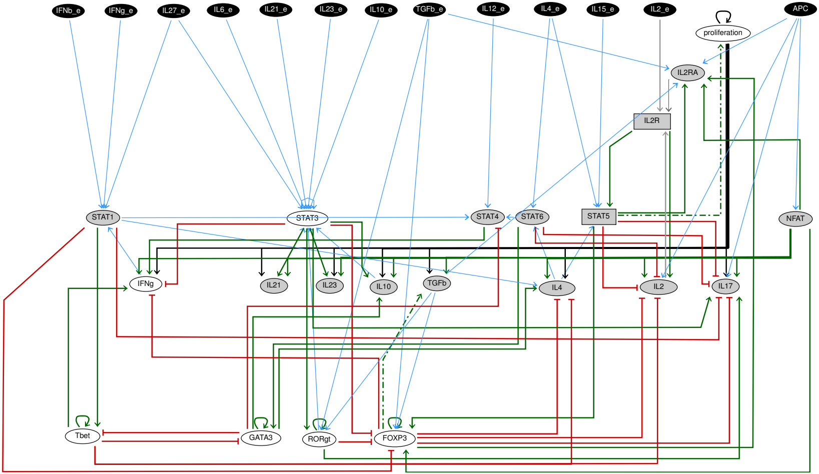

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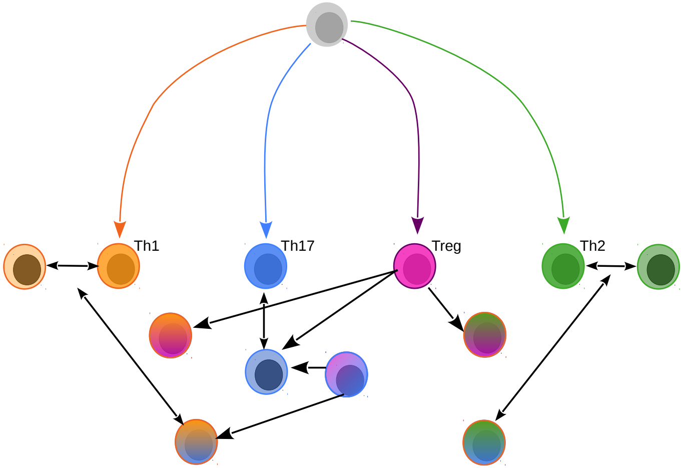

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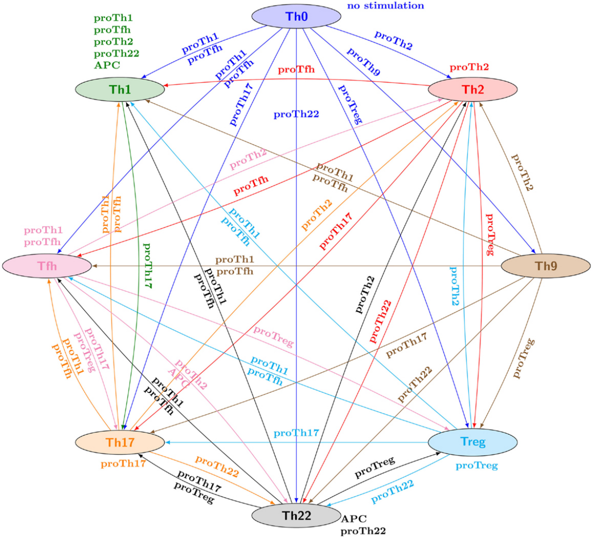

W Abou-Jaoudé et al. *Front Bioeng Biotechnol* (2014)

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Conclusion and prospects

An efficient reduction method

- Automated reduction
- Preserved attractors
- Well defined dynamical impact
- Implementation available
- Applied in some published models

... with some low-hanging fruits

- Automated "safe reductions"
  Extend to longer paths
- Reduction for static analysis:
  do NOT generate complex functions
- Find possible orders

Acknowledgements & Collaborations

IGC, Lisbonne

Claudine Chaouiya
Pedro Monteiro
Jorge Carneiro

IML, Marseille

Elisabeth Remy

IBENS – Curie, Paris

Denis Thieffry
Wassim Abou-Jaoudé